PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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- RECEIVED -
09 AUG. 2004

PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	06.08.2004
Applicant's or agent's file reference UNI-003-PCT	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/14567	18.12.2003	18.12.2002

International Patent Classification (IPC) or both national classification and IPC
C07J7/00

Applicant
UNIBIOSCREEN S.A.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 18.04.2005

Name and mailing address of the international preliminary examining authority:

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Authorized Officer
Wörth, C

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-72 as originally filed

Claims, Numbers

1-20 as originally filed

Drawings, Sheets

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 20 with respect to IA

   because:

   ☒ the said international application, or the said claims Nos. 20 with respect to IA relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	Yes: 1-20
Inventive step (IS)	Claims	No: 1-20
Industrial applicability (IA)	Claims	Yes: 1-19

2. Citations and explanations

   see separate sheet

1. **Re Item I** ***(Basis of the report)***

Reference is made to the following documents:

D1: MODI, SANDEEP P. ET AL: "Conjugate addition of Grignard reagents to enones and dienones" JOURNAL OF ORGANIC CHEMISTRY (1989), 54(10), 2317-21, XP002242748

D2: CIOBANU, L. C. ET AL: "Synthesis and steroid sulfatase inhibitory activity of C19- and C21-steroidal derivatives bearing a benzyl-inhibiting group" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY (2001), 36(7-8), 659-671, XP004372876

D3: R. P. BOIVIN ET AL.: "Structure-Activity Relationship of 17alpha-Derivatives of Estradiol as Inhibitors of Steroid Sulfatase" J. MED. CHEM., vol. 43, 2000, pages 4465-4478, XP002232869

D4: ENDO, YASUYUKI ET AL: "Oxygenated cholesterols as ligands for cytosolic-nuclear tumor promoter binding protein: Yakkasteroids" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS (1993), 194(3), 1529-35, XP002232867

D5: JP 06 321782 A (SHUDO KOICHI, JAPAN) 22 November 1994 (1994-11-22)

D6: BERGSTROM, CARL P. ET AL: "Inhibition of cholesterol side-chain cleavage. Part 5. Synthesis of 22-(p-chlorophenyl)cholesterol analogs" DRUG DESIGN AND DELIVERY (1991), 7(4), 259-68, XP001079777

2. **Re Item III** ***(Non-establishment of opinion with regard to novelty, inventive step and industrial applicability)***

Claim 20 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

3. **Re Item V** ***(Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement)***

3.1 Novelty

The subject-matter of the present application differs from

- D1 in view of the **proviso** at the end of present claim 1 excluding compound 7c of D1

- D2-D6 in view of the **benzyl-like substitution at position 16** of the steroid skeleton.

The requirements of novelty are fulfilled.

3.2 Inventive step

At present, document D2 is considered as **closest prior art**. This document discloses C19 and C21 steroidal derivatives bearing a benzyl-group having inhibitory activity on steroid sulphatase (see section conclusions, page 664) being consequently useful in the treatment of hormone sensitive cancers (see abstract).

In view of this document, the **problem to be solved** can be regarded as the provision of further compounds having the same biological activity as those in D2.

The **solution** consists in compounds of formula IB. In view of example 3, table D and E, the problem is at present considered as solved at least for one compound claimed.

However, the solution is considered as **obvious** in the light of the combined technical teaching of documents D2 and D3. Document D3 teaches the introduction of a benzyl **at position 16 of a steroid skeleton (see scheme 3, compounds 27 and 28 and table 4) in order to achieve the desired biological activity**.

Accordingly, the provision of compounds of formula IB of the present application characterized by a different steroid skeleton and a variable linker (see definition of present "n") is an obvious design possibility for the skilled person having knowledge of the teaching of D2 and D3 in order to solve the problem posed.

As far as the scope of the claims is concerned, the Applicant's attention is drawn to the fact that only such compounds can be claimed which represent a solution of the problem underlying the application in suit. The extent of a reasonable generalisation depends on the credibility that substantially all the alternatives claimed must be a solution to the problem. Extremely broad generalisations like e.g. the definition of "X_1, X_2, R1 and R2" (wherein an activity has only be shown for three individual compounds) in claim 1 are in contradiction to the basis of qualitative structure-activity-relationships. Taking into account the relevant state of the art and the common knowledge, it appears to be not predictable, that all

alternatives would achieve the technical effect.
The Applicant is invited to submit all information available to him to substantiate that **all claimed compounds** represent a solution to the problem underlying this application or - if necessary - to **restrict** the claims to such compounds which illustrate respectable patentable effects).

The present subject-matter does not fulfill the requirements of inventive step.

3.3 Industrial applicability

For the assessment of the present claim 20 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.